



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY  
WASHINGTON, D.C. 20460

OFFICE OF  
PREVENTION, PESTICIDES, AND  
TOXIC SUBSTANCES

**MEMORANDUM**

**DATE:** December 23, 1999

**SUBJECT:** **Etridiazole.** Revised Toxicology Chapter of the Reregistration Eligibility Decision. Chemical Number 084701. DP Barcode D262018.

**FROM:** Michelle M. Centra, Pharmacologist  
Reregistration Branch III  
Health Effects Division (7509C)

**THROUGH:** Steven Knizner, Branch Senior Scientist  
Reregistration Branch III  
Health Effects Division (7509C)

**TO:** Danette Drew, Risk Assessor  
Reregistration Branch III  
Health Effects Division (7509C)

and

Roberta Farrell, Chemical Review Manager  
Kathy Monk, Branch Chief  
Reregistration Branch II  
Special Review and Reregistration Division (7508C)

Attached please find the Toxicology Chapter of the Reregistration Eligibility Decision for Etridiazole.

## 1.0 EXECUTIVE SUMMARY

### *Hazard Assessment*

The toxicity data base for etridiazole contains several mammalian toxicity studies that do not meet the requirements of the Subdivision F guideline requirements for a food-use chemical (40 CFR Part 158.340). However, the Hazard Identification Assessment Review Committee (HIARC) evaluated the acceptable studies available in the data base and established an acute and a chronic reference dose (RfD) as well as doses and endpoints for short-, intermediate- and long-term dermal and inhalation exposure scenarios. The HIARC also evaluated available studies to determine if there is a special sensitivity for infants and children.

Etridiazole has a low order of acute toxicity via oral, dermal, or inhalation routes (Toxicity Category III or IV), produces mild irritation to the eyes (Toxicity Category III) and is a skin sensitizer.

Subchronic mammalian toxicity studies submitted to the Agency do not meet the Subdivision F guideline requirements for a food-use chemical (40 CFR Part 158.340) and therefore these studies were determined to be unacceptable for regulatory purposes.

Following chronic exposure in rats and dogs, the primary target for etridiazole toxicity is the liver. Systemic toxicities observed in the two-year rat carcinogenicity study include increased absolute and relative liver weights, hepatocytomegaly, spongiosis hepatis, clear, basophilic, and eosinophilic hepatocellular alterations, hepatic centrilobular pigmentation and cholangiectasis. Additional toxicities observed in this study were decreased body weight gains, renal tubule cell karyomegaly and testicular interstitial cell hyperplasia. In the two-year chronic toxicity study in dogs, systemic toxicity in both sexes manifested as increased serum aspartate aminotransferase (SGOT) and serum alkaline phosphatase (ALK;SAP) activity, increased relative liver weights, liver pathology consistent with cholestatic hepatis, secondary bile nephrosis and increased prothrombin time.

There was no quantitative or qualitative evidence of increased susceptibility in the fetuses or the offspring of rats or rabbits following pre- and/or postnatal exposure to etridiazole. In the prenatal developmental toxicity studies in rats and rabbits and the multi-generation reproduction study in rats, any observed toxicity to the fetuses or offspring occurred at equivalent or higher doses than did toxicity to parental animals. Although the HIARC determined that the multi-generation reproduction study in rats was an unacceptable-guideline study and not adequate for regulatory purposes, the study results suggest that the observed offspring effects in this study occurred only at a treatment level which resulted in parental toxicity.

Although there is no indication of neurotoxicity in any of the mammalian toxicity studies submitted, most of these studies are not adequate for regulatory purposes. Hence, there are insufficient data to assess the neurotoxic potential of etridiazole. The request for neurotoxicity studies (including a developmental neurotoxicity study in rats) is placed in reserve status pending submission and evaluation of a repeat multi-generation reproduction study in rats and a chronic toxicity study in dogs.

Etridiazole induced genotoxic responses in several mutagenicity assays and is considered a mutagen. Positive responses occurred in the gene mutation assay in *Salmonella typhimurium*, in

the *in vitro* cytogenetics assay in Chinese hamster ovary cells and in the two *in vitro* sister chromatid exchange assays in Chinese hamster ovary cells.

Etridiazole is classified as a Group B2 chemical (probable human carcinogen) based on the occurrence of multiple tumor types in male and female rats (tumor sites noted were the liver, bile duct, mammary gland, thyroid, and testes), including the induction of a rare bile duct tumor (cholangiocarcinoma). A linear, low-dose approach ( $Q_1^*$ ) is used for human risk characterization. The most potent unit risk  $Q_1^*$ , based on the thyroid follicular cell combined adenomas/carcinomas in male rats, is  $3.33 \times 10^{-2} \text{ (mg/kg/day)}^{-1}$  in human equivalents [converted from animals to humans by use of the  $(\text{mg/kg body weight})^{3/4}$  interspecies scaling factor].

**A FQPA Safety Factor is required for all population subgroups** for etridiazole because of the lack of an acceptable multi-generation reproduction study in rats, which could identify potential reproductive effects to the parental animals or to the offspring following pre/post natal exposure to etridiazole. However, **the FQPA safety factor was reduced to 3x** because: (i) there is no quantitative or qualitative indication of increased susceptibility in the prenatal developmental toxicity studies in rats and rabbits (ii) although the multi-generation reproduction study in rats was determined to be an unacceptable-guideline study and not adequate for regulatory purposes by the HIARC, the study results suggest that the observed offspring effects in this study occurred only at a treatment level which resulted in parental toxicity and (iii) adequate data are available or conservative modeling assumptions are used to assess the potential for dietary (food and drinking water) exposure to infants and children.

An acute reference dose (RfD) was not determined for the general population because an appropriate endpoint attributable to a single exposure (dose) was not identified in oral toxicity studies (including the developmental toxicity studies in rats and rabbits). Therefore, an acute dietary risk assessment is not required for the general population.

However, an acute reference dose (aRfD) of 0.15 mg/kg/day was determined for the subpopulation group, females 13-50 years, based on the NOAEL of 15 mg/kg/day in the developmental toxicity study in rabbits and an uncertainty factor of 100 (10x for inter-species extrapolation and 10x for intra-species variation). The skeletal malformations/variations (missing sternebrae and tail defects) observed in the fetuses at 45 mg/kg/day are presumed to occur after a single exposure (dose) and therefore, the endpoint is appropriate for this risk assessment. As per the recommendation of the FQPA Safety Factor Committee (6/3/99), **the 3x FQPA Safety Factor is not applied to the population subgroup, females 13-50, for the estimation of acute dietary risk.** The Committee made this recommendation because no increased susceptibility was seen following *in utero* exposure, and in addition, the results of the multi-generation reproduction study may not provide an endpoint of concern (i.e., an *in utero* effect) that would be applicable to females of child-bearing age (13-50 years old).

As per current policy, a reference dose (RfD) modified by a FQPA safety factor is referred to as a population adjusted dose (PAD). Since the FQPA safety factor is not applicable to the acute RfD, **the acute RfD and the acute PAD are numerically equivalent for the subpopulation, females 13-50 years old.**

A chronic reference dose (RfD) of 0.016 mg/kg/day was established based on the NOAEL of 4.8 mg/kg/day from the two-year carcinogenicity study in rats and the application of an uncertainty factor of 300 (10x for intraspecies extrapolation, 10x for interspecies

variation and 3x applied under FIFRA for the lack of an acceptable chronic study). The LOAEL in this study was 30.43 mg/kg/day based on increased absolute and relative liver weights, renal tubule cell karyomegaly, hepatocytomegaly and spongiosis hepatitis in male rats. As per the recommendation of the FQPA Safety Factor Committee (6/3/99), the **3x FQPA safety factor is applied to chronic dietary risk assessment** because uncertainty exists due to the lack of an acceptable multi-generation reproduction study in rats, which could identify potential toxicities following exposure to etridiazole in the offspring and/or the parental animals. Therefore, the **chronic population adjusted dose (cPAD) is 0.005 mg/kg/day**.

The HIARC identified doses and endpoints for short-, intermediate-, and long-term dermal and inhalation exposures. For short-term dermal exposure and risk assessments, the rat developmental NOAEL of 15 mg/kg/day was selected from the developmental toxicity study in rabbits. This dose and endpoint were selected because: 1) the developmental effects are considered short-term and thus are appropriate for this exposure period (i.e., 1-7 days) of concern, 2) the reproductive/fetal parameters are not evaluated in the dermal toxicity study and thus the consequences of these effects cannot be ascertained for the dermal route of exposure and 3) this endpoint will provide adequate protection for the subpopulation of females 13+ years old, i.e., pregnant workers (the population subgroup of concern is females of child-bearing age [13-50 years old]). In addition, the two 21-day dermal toxicity studies in rabbits were classified by the HIARC unacceptable because of major deficiencies.

Since no inhalation studies are available (with the exception of an acute inhalation toxicity study) in the etridiazole data base, the oral developmental NOAEL of 15 mg/kg/day was also selected and is considered appropriate for a short-term inhalation exposure (1 to 7 days) and risk assessment. This endpoint will provide adequate protection for the subpopulation of females 13-50 years old, i.e., pregnant workers (the population subgroup of concern is females of child-bearing age [13-50 years old]).

For intermediate- and long-term dermal and inhalation exposure risk assessments, the NOAEL of 4.8 mg/kg/day was selected from the two-year carcinogenicity study in rats and is considered appropriate for these exposure scenarios due to the lack of acceptable subchronic studies in the etridiazole data base. The developmental NOAEL (15 mg/kg/day) is not recommended for this time period since the lower NOAEL (4.8 mg/kg/day) in the two-year carcinogenicity study in rats is more protective for the intermediate-term dermal and inhalation exposure scenarios and risk assessments.

No dermal absorption study is available in the etridiazole toxicity data base. In addition, the dermal toxicity studies submitted to the Agency were evaluated and determined to be inadequate for regulatory purposes. Therefore, the default value of 100% dermal absorption equivalent to oral absorption was used in this risk assessment. Also, a default value of 100% was used for inhalation risk assessments.

A MOE of 100 (10x for interspecies extrapolation and 10x for intraspecies variation) is adequate for short- and intermediate-term dermal and inhalation occupational risk assessments. A MOE of 300 is required for long-term dermal and inhalation occupational risk assessments (10x for interspecies extrapolation, 10x for intraspecies variation and 3x under FIFRA for the lack of an acceptable chronic study).

Although there are no registered uses of etridiazole in or around the home, it is registered for use

on golf courses. Hence, there is a potential for short-term non-occupational exposure to adults and children entering golf courses that have been treated with etridiazole. A risk assessment for this exposure scenario for the general population, including infants and children, was not conducted since the short-term dermal toxicological endpoint of concern was based on an *in utero* effect not applicable to these subgroups. A risk assessment was conducted for female golfers of child-bearing age (13-50 years old) using the developmental NOAEL of 15 mg/kg/day.

### **3.0 HAZARD CHARACTERIZATION**

#### **3.1 HAZARD PROFILE**

Etridiazole has a low order of acute toxicity via oral, dermal, or inhalation routes (Toxicity Category III or IV), produces mild irritation to the eyes (Toxicity Category III) and it is a skin sensitizer in the Beuhler dermal sensitization assay.

Subchronic mammalian toxicity studies submitted to the Agency do not meet the current Subdivision F guideline requirements for a food-use chemical (40 CFR Part 158.340) and therefore these studies were determined to be unacceptable for regulatory purposes. Hence, subchronic toxicity studies were not used in this risk assessment.

Following chronic exposure in rats, the primary target for etridiazole toxicity is the liver. At 640 ppm (30.43 mg/kg/day in males, 38.45 mg/kg/day in females), systemic toxicities observed in the 2-year rat carcinogenicity study included decreased body weight gain in females, increased absolute and relative liver weight in males, hepatocytomegaly in males, spongiosis hepatitis in males, clear, basophilic, and eosinophilic hepatocellular alterations in both sexes, hepatic centrilobular pigmentation in females, cholangiectasis in females, renal tubule cell karyomegaly in males and females and testicular interstitial cell hyperplasia in males. In the two year, non guideline chronic toxicity study with dogs, systemic toxicities in both sexes manifested as increased serum aspartate transferase (SGOT) and serum alkaline phosphatase (ALK;SAP) activity, increased relative liver weights, liver pathology consistent with cholestatic hepatitis with secondary bile nephrosis and increased prothrombin time at a dose level of 25 mg/kg/day.

In accordance with the Agency's Proposed Guideline for Carcinogen Risk Assessment (April 11, 1993), the HED Cancer Peer Review Committee (CPRC) classified etridiazole as a Group B2 carcinogen (Probable Human Carcinogen). This classification is based on the following factors: (i) occurrence of multiple tumor types in male and female rats (tumor sites noted were the liver, bile duct, mammary gland, thyroid, and testes) including the induction of a rare bile duct tumor (cholangiocarcinoma), and (ii) non-neoplastic lesions observed in similar target organs that lend support to the association of etridiazole exposure with the induction of tumors; increased absolute and relative liver weight (males), hepatocytomegaly (males); clear, basophilic, and eosinophilic cellular alterations (males and females); cholangiectasis (females); centrilobular pigmentation (females); spongiosis hepatitis of the liver (males); and testicular interstitial cell hyperplasia (males) and (iii) positive mutagenicity data. The carcinogenicity study in mice was determined to be unacceptable and not adequate for assessment of the carcinogenic potential of etridiazole in this species.

For the purpose of human risk characterization, the CPRC concluded that a low dose extrapolation model ( $Q_1^*$ ) be applied to the experimental animal tumor data. A quantification of risk was recommended for each sex using all tumor bearing animals with tumor types that are

statistically significant for that sex. In addition, a separate risk quantification was performed on the rare bile duct tumor, cholangiocarcinoma, for each sex. The estimates of unit risk,  $Q_1^*$ , were obtained by application of the Multi-Stage model, Tox\_Risk program, Version 3.5, K. Crump, 1994 (Memorandum: L. Brunzman, 2/10/99). Following these calculations, the most potent unit risk  $Q_1^*$ , based on the occurrence of thyroid follicular cell combined adenomas/carcinomas in male rats, is  $3.33 \times 10^{-2} \text{ (mg/kg/day)}^{-1}$  in human equivalents [converted from animals to humans by use of the  $(\text{mg/kg body weight})^{3/4}$  cross species scaling factor].

There was no quantitative or qualitative evidence of increased susceptibility in rats or rabbits following pre- and/or postnatal exposure to etridiazole. In the developmental toxicity study in rats, reduced fetal body weights and late resorptions at 75 mg/kg/day occurred in the presence of maternal toxicity (increased mortality, decreased absolute body weights and body weight gains and anogenital matting at dose levels of 30 mg/kg/day). In the prenatal developmental toxicity study in rabbits, both fetal and maternal toxicity were observed at the LOAEL of 45 mg/kg/day. At this dose, increased mortality and body weight decreases were observed in maternal animals and fetal toxicity consisted of reduced fetal body weights, decreased viability and an increase in the incidence of skeletal malformations/variations.

In the multi-generation reproduction study in rats, offspring toxicity (reduced fetal body weights) were observed only at a dose (32 mg/kg/day) which resulted in evidence of parental toxicity (reduced parental body weights). However, the HIARC determined that this study is unacceptable and not adequate for regulatory purposes.

Although mammalian neurotoxicity studies for etridiazole have not been conducted, these special neurotoxicity studies (i.e., delayed neurotoxicity in the hen, acute neurotoxicity, subchronic neurotoxicity and/or developmental neurotoxicity) are not required at the present time because there is no evidence of neurotoxicity in the available guideline toxicity studies. The request for neurotoxicity studies, specifically, a developmental neurotoxicity study in the rat, is placed in reserve status pending submission and evaluation of a new multi-generation reproduction study in rats and a chronic toxicity in dogs.

Etridiazole induced positive responses in both the absence and presence of S9 metabolic activation in the sister chromatid exchange assays in Chinese hamster ovary cells and in one *in vitro* cytogenetic chromosomal aberration assay in Chinese hamster ovary cells. In the absence of S9 metabolic activation, etridiazole induced reverse gene mutations in *Salmonella typhimurium*. There was, however, no evidence of a positive effect in an *in vivo* cytogenetics micronucleus assay in mice and in a second *in vitro* cytogenetics chromosomal aberration assay in Chinese hamster ovary cells. Based on the positive mutagenic and genotoxic responses observed in the mutagenicity battery, etridiazole is considered a mutagen.

Analysis of whole body elimination in male and female rats indicated that etridiazole is rapidly absorbed and peak elimination occurs within 48 hours of dosing. The metabolite profile in urine was similar between sexes and among the four dose groups; metabolites were identified as etridiazole carboxylic acid, ethyl (aminocarbonyl) carbamate, N-carboxy oxamic acid and N-acetyl cysteinyl conjugate of etridiazole.

No dermal absorption study is available in the etridiazole toxicity data base. In addition, the dermal toxicity studies submitted to the Agency were evaluated and determined to be inadequate for regulatory purposes. Therefore, the default value of 100% dermal absorption was used in this

risk assessment.

There are several data gaps for the standard Subdivision F Guideline requirements for a food-use chemical (40 CFR Part 158.340); a multi-generation reproduction study in rats (protocol to include early thyroid measurements; pre-mating, adults and pups) and a chronic toxicity study in dogs (that meets the chronic toxicity test guidelines). In addition, there is insufficient data to assess the neurotoxic potential of etridiazole. However, the request for additional studies (i.e., delayed neurotoxicity study in the hen, acute neurotoxicity study, subchronic neurotoxicity study and/or developmental neurotoxicity study) is placed in reserve status pending submission and evaluation of a repeat multi-generation reproduction study in rats and a chronic toxicity study in dogs.

Tables 1 and 2 summarize the acute, subchronic and chronic toxicity of etridiazole.

<b>TABLE 1. Acute Toxicity Profile for Etridiazole (Terrazole)</b>					
<b>Guideline</b>	<b>MRID#</b>	<b>Study Type*</b>	<b>Results</b>	<b>Tox. Cat.</b>	<b>Classification</b>
870.1100 (§81-1)	43724501	Acute Oral - Rat (2/8/94)	LD <sub>50</sub> (males) = 1141 mg/kg LD <sub>50</sub> (females) = 945 mg/kg LD <sub>50</sub> (males and females combined) = 1028 mg/kg	III	Acceptable-Guideline
870.1200 (§81-2)	43724502	Acute Dermal - Rabbit (2/8/94)	LD <sub>50</sub> (males and females combined) > 5000 mg/kg	IV	Acceptable-Guideline
870.1300 (§81-3)	43724503	Acute Inhalation - Rat (2/8/94)	LC <sub>50</sub> (males and females combined) > 5.7 mg/L	IV	Acceptable-Guideline
870.2400 (§81-4)	43724504	Primary Eye Irritation - Rabbit (2/8/94)	Moderate Eye Irritant	III	Acceptable-Guideline
870.2500 (§81-5)	43724505	Primary Dermal Irritation - Rabbit (2/8/94)	Non Irritant	IV	Acceptable-Guideline
870.2600 (§81-6)	43724506	Dermal Sensitization - Guinea pig-unspecified purity of terrazole technical (1/22/93)	Moderate Dermal Sensitizer	N/A	Acceptable-Guideline

\*The percent active ingredient of the technical test material used in each of the acute toxicity studies was reported as 98.6% a.i., unless specified otherwise.

<b>TABLE 2. Subchronic and Chronic Toxicity Profile for Etridiazole (Terrazole)</b>			
<b>Guideline</b>	<b>MRID#</b>	<b>Study Type*</b>	<b>Results</b>
870.3100 ('82-1a)	00001700	90-Day Oral Toxicity - Rat, technical; 50% a.i. (1964)	NOAEL (males, females) = 312 ppm LOAEL (males, females) = 625 ppm based on increased liver to body weight ratios and growth depression  Classification: Unacceptable-Guideline (not upgradable)
870.3150 ('82-1b)	00001699	90-Day Oral Toxicity - Dog, technical; 50% a.i. (1964)	NOAEL (males, females) > 1600 ppm LOAEL (males, females) = not established  Classification: Unacceptable-Guideline (not upgradable)
870.3200 ('82-2b)	00063303	21-Day Dermal Toxicity - Rabbit, unspecified purity (1/11/65)	NOAEL (males, females) = not established LOAEL (males, females) = not established  Classification: Unacceptable-Guideline (not upgradable)
870.3200 ('82-2b)	00114197	21/28-Day Dermal Toxicity - Rabbit, Terrachlor Super X Formulation (6/65)	NOAEL (males, females) = 0.65 ml/kg/day LOAEL (males, females) = 1.30 ml/kg/day based on increased kidney to body weight ratios  Classification: Unacceptable-Guideline (not upgradable)
<b>Chronic Toxicity</b>			
870.4100 ('83-1b)	00001697	Chronic Toxicity - Dog (8/5/68)	NOAEL (males, females) = 2.5 mg/kg/day LOAEL (males, females) = 25 mg/kg/day based on increased SGOT and SAP activity, increased liver to body weight ratios, liver pathology consistent with cholestatic hepatitis, secondary bile nephrosis and increased prothrombin time.  Classification: Acceptable-Non Guideline
870.4200 ('83-2a)	40747901	Oncogenicity -Rat (6/23/88)	NOAEL = 100 ppm (4.8/5.9 mg/kg/day, males/females) LOAEL = 640 ppm (30.43/38.45 mg/kg/day, males/females) based on decreased body weight gain (females), increased liver weight (absolute and relative), renal tubule cell karyomegaly (males, females), hepatocytomegaly (males), spongiosis hepatitis (males), cholangiectasis (females) and centrilobular pigmentation (females).  Etridiazole has carcinogenic potential in the livers of female rats, and the testes of male rats and possibly in the thyroid of male rats. It can also induce cholangiocarcinoma, a rare tumor, predominantly in female rats.  Classification: Acceptable-Guideline

**TABLE 2. Subchronic and Chronic Toxicity Profile for Etridiazole (Terrazole)**

Guideline	MRID#	Study Type*	Results
870.4200 (* 83-2b)	00093744	Oncogenicity -Mouse (3/14/81)	<p>NOAEL (males, females) = 640 ppm (91 mg/kg/day)  LOAEL = 1280 ppm (183 mg/kg/day) based on minor decreases in body weight and food efficiency, stomach hyperkeratosis, nephritis and adrenal and ovarian degeneration in females, lung hyperplasia in males, and spleen alterations in both sexes</p> <p>Under conditions of this study, there was equivocal evidence of carcinogenicity based on an increased incidence of alveologenic carcinoma female mice.</p> <p>Classification: Unacceptable-Guideline (not upgradable)</p>
<b>Developmental/Reproductive Toxicity</b>			
870.3700 (* 83-3a)	00120415	Developmental Toxicity - Rat (5/27/82)	<p><u>Maternal Toxicity</u>  NOAEL = 10 mg/kg/day  LOAEL = 30 mg/kg/day based on clinical signs of toxicity (anogenital matting)</p> <p><u>Developmental Toxicity</u>  NOAEL = 30 mg/kg/day  LOAEL = 75 mg/kg/day based on decreased fetal body weights and increased late resorptions</p> <p>Classification: Acceptable-Guideline</p>
870.3700 (* 83-3b)	00104999	Developmental Toxicity - Rabbit (5/22/79)	<p><u>Maternal Toxicity</u>  NOAEL = 15 mg/kg/day  LOAEL = 45 mg/kg/day based on increased mortality and decreased body weights</p> <p><u>Developmental Toxicity</u>  NOAEL = 15 mg/kg/day  LOAEL = 45 mg/kg/day based on reduced fetal body weights, viability and increased incidence of external and skeletal malformations/variations</p> <p>Classification: Acceptable-Guideline</p>
870.3800 (* 83-4)	00001698	Multigeneration Reproductive Toxicity - Rat (1968)	<p><u>Systemic/Parental/Offspring Toxicity</u>  NOAEL = 80 ppm (4 mg/kg/day)  LOAEL = 640 ppm (32 mg/kg/day) based on reduced body weights of adult animals and pups</p> <p><u>Reproductive Toxicity</u>  NOAEL ≥ 640 ppm (32 mg/kg/day)  LOAEL &gt; 640 ppm (32 mg/kg/day), not established</p> <p>Classification: Unacceptable-Guideline (not upgradable)</p>
<b>Mutagenicity</b>			
870.5100 (* 84-2)	00093742	Gene Mutation in <i>Salmonella typhimurium</i> and <i>Escherichia coli</i> (11/2/81)	<p><b>Negative.</b> Etridiazole did not induce a mutagenic or genotoxic effect under any test condition in any assay.</p> <p>Classification: Unacceptable-Guideline (not upgradable)</p>

TABLE 2. Subchronic and Chronic Toxicity Profile for Etridiazole (Terrazole)			
Guideline	MRID#	Study Type*	Results
870.5100 ('84-2)	00073206	Gene Mutation in <i>Salmonella typhimurium</i> (10/77)	<p><b>Positive.</b> Etridiazole induced a mutagenic response in <i>Salmonella typhimurium</i> strain TA100 at noncytotoxic doses of 0.02, 0.06 and 0.2 µg/plate -S9 activation. There was, however, no evidence of a mutagenic effect in the presence of S9 activation. Etridiazole was not mutagenic in strain TA98.</p> <p>Classification: Acceptable-Nonguideline</p>
870.5300 ('84-2)	00093743	Gene Mutation/ <i>In vitro</i> mammalian cell assay in Chinese hamster ovary cells (11/10/81)	<p><b>Negative.</b> Etridiazole did not induce a mutagenic effect in Chinese hamster ovary cells at noncytotoxic concentrations of 0.001-0.008% (equivalent to 10-80 µg/mL) -S9 activation and 0.001-0.005% (equivalent to 10-50 µg/mL) +S9 activation after a 16 or 5 hour incubation period, respectively.</p> <p>Classification: Acceptable-Guideline</p>
870.5385 ('84-2)	41837501	Cytogenetics/ <i>In vivo</i> mouse micronucleus assay (10/30/85)	<p><b>Negative.</b> There was no evidence of either a clastogenic or aneugenic effect in male and female mice administered 1000 mg/kg etridiazole at any sacrifice time.</p> <p>Classification: Acceptable-Guideline</p>
870.5900 ('84-2)	00120414	Other Mutagenic Mechanisms/ <i>In vitro</i> Sister Chromatid Exchange in Chinese hamster ovary cells (1/26/81)	<p><b>Positive.</b> Etridiazole induced increases in the frequency of sister chromatid exchanges per cell at concentrations of 0.002 to 0.005% (equivalent to 20 to 50 µg/mL) -S9 activation and 0.002 and 0.003% (equivalent to 20 and 30 µg/mL) +S9 activation after a 27.5 or 4 hour incubation period, respectively.</p> <p>Classification: Acceptable-Guideline</p>
870.5375/ 870.5900 ('84-2)	00120416	Other Mutagenic Mechanisms/ <i>In vitro</i> Cytogenetics/ Sister Chromatid Exchange in Chinese hamster ovary cells (6/4/82)	<p><b>Positive.</b> Etridiazole induced increases in the frequency of sister chromatid exchanges per cell at concentrations of 0.003-0.005% (equivalent to 10-50 µg/mL) -S9 after a 27-28 hour incubation period. In addition, etridiazole induced increases in the frequency of cells with structural chromosomal aberrations at concentrations of 0.005% and 0.006% (equivalent to 50 and 60 µg/mL) -S9 activation and 0.003, 0.005 and 0.006% (equivalent to 30, 50 and 60 µg/mL) +S9 activation after a 6 or 2 hour incubation period, respectively.</p> <p>Classification: Acceptable-Guideline</p>
Metabolism			
870.7485 ('85-1)	43654801	Metabolism - Rat (4/28/95)	<p>Etridiazole is rapidly absorbed and peak elimination occurs within 48 hours of dosing. The metabolite profile in urine was similar between sexes and among the four dose groups; metabolites were identified as etridiazole carboxylic acid, ethyl (aminocarbonyl) carbamate, N-carboxy oxamic acid and N-acetyl cysteinyl conjugate of etridiazole.</p> <p>Classification: Acceptable-Guideline</p>

\*The percent active ingredient of the test material used in the subchronic and chronic toxicity studies ranged from

93 to 99%, unless specified otherwise.

## 3.2 FQPA CONSIDERATIONS

The FQPA Safety Factor Committee (SFC) (6/3/99) concluded that a safety factor is required for etridiazole since there is uncertainty due to the data gaps for the 2-generation reproductive study in rats.

The FQPA SFC recommended that the **FQPA safety factor** for protection of infants and children (as required by FQPA) be **reduced to 3x** because:

- ▶ there is no quantitative or qualitative indication of increased susceptibility in the prenatal developmental toxicity studies in rats and rabbits
- ▶ although the multi-generation reproduction study in rats was determined to be an unacceptable-guideline study and not adequate for regulatory purposes by the HIARC, it is noted that the observed offspring effects in this study occurred only at a treatment level which resulted in parental toxicity
- ▶ adequate data are available or conservative modeling assumptions are used to assess the potential for dietary (food and drinking water) exposure to infants and children.

Additionally, the FQPA SFC recommended that the weight-of-evidence for the FQPA safety factor recommendation be re-evaluated after all data requirements for etridiazole have been satisfied.

### *Application of the Safety Factor*

#### Population Subgroups

The FQPA safety factor is **applicable to all population subgroups** since there is uncertainty due to the data gap for the two-generation reproduction study in rats which could identify potential reproductive effects to the parental animals or to the offspring following exposure to etridiazole.

### *Risk Assessment Scenarios*

The FQPA safety factor for etridiazole is **applicable to chronic dietary risk assessment and all residential (non-occupational) risk assessments** since there is uncertainty due to the data gap for the two-generation reproduction study in rats which could identify potential reproductive effects to the parental animals or to the offspring following exposure to etridiazole. The safety factor is **not applicable to acute dietary risk assessment** since no increased susceptibility was demonstrated following *in utero*

exposure and the two-generation reproductive study may not provide information on the potential for effects occurring after a single dose (exposure).

### **3.3 Other FQPA Considerations**

#### **3.3.1. Cumulative Risk**

EPA does not have, at this time, available data to determine whether etridiazole has a common mechanism of toxicity with other substances or how to include this pesticide in a cumulative risk assessment. For the purposes of this reregistration action, therefore, EPA has not assumed that etridiazole has a common mechanism of toxicity with other substances.

On this basis, the petitioner must submit, upon EPA's request and according to a schedule determined by the Agency, such information as the Agency directs to be submitted in order to evaluate issues related to whether etridiazole share(s) a common mechanism of toxicity with any other substance and, if so, whether any tolerances for etridiazole need to be modified or revoked.

#### **3.3.2. Endocrine Disruption**

The Food Quality Protection Act (FQPA; 1996) requires that EPA develop a screening program to determine whether certain substances (including all pesticides and inerts) may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or such other endocrine effect....@ EPA has been working with interested stakeholders, including other government agencies, public interest groups, industry and research scientists to develop a screening and testing program as well as a priority setting scheme to implement this program. The Agency's proposed Endocrine Disrupter Screening Program was published in the Federal Register of December 28, 1998 (63 FR71541). The Program uses a tiered approach and anticipates issuing a Priority List of chemicals and mixtures for Tier 1 screening in the year 2000. As the Agency proceeds with implementation of this program, further testing of etridiazole and its end-use products for endocrine effects may be required.

### 3.4 DOSE RESPONSE ASSESSMENT

Table 3 presents the summary of toxicology doses and endpoints for etridiazole risk assessment.

TABLE 3: SUMMARY OF TOXICOLOGY ENDPOINT AND DOSES FOR ETRIDIAZOLE (TERRAZOLE)		
EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT/STUDY/RATIONALE/UF/MOE
Acute Dietary (Females 13-50)	NOAEL=15	Reduced fetal body weights, decreased viability and external and skeletal malformations/variations in the rabbit developmental toxicity study. The skeletal malformations/variations (missing sternbrae and tail defects) are presumed to occur after a single exposure (dose) and thus are appropriate for acute risk assessment. Since the selected NOAEL is based on a developmental endpoint, it is applicable only to the population subgroup, females 13-50 years old. The 100x uncertainty factor includes 10x for interspecies extrapolation and 10x for intraspecies variation. A FQPA safety factor was not applicable to acute dietary risk assessment since no increased susceptibility was demonstrated following <i>in utero</i> exposure and the multi-generation reproduction study in rats may not provide information on the potential for adverse effects occurring after a single exposure (dose).
	UF=100 FQPA SF=1	
	Acute RfD = 0.15 mg/kg    Acute PAD = 0.15 mg/kg	
Acute Dietary (General Population )	An appropriate endpoint attributable to a single exposure (dose) was not identified in oral toxicity studies (including the developmental toxicity studies in rats and rabbits) that is applicable to subpopulations other than females of childbearing age (13-50 years old).	
Chronic Dietary	NOAEL=4.8	Increased absolute and relative liver weights, renal tubule cell karyomegaly, hepatocytomegaly and spongiosis hepatitis in the two-year carcinogenicity study in rats. The HIARC re-assessed the RfD and determined that the two-year chronic toxicity study in dogs previously used to establish this value does not meet the current guideline requirements. Due to the numerous deficiencies observed as a result of the age of this chronic toxicity study (1966-1969), it is not adequate for establishing the RfD. Consequently, the two-year rat carcinogenicity study was selected for this exposure scenario. The uncertainty factor includes 10x for interspecies extrapolation, 10x for intraspecies variation, 3x for the FQPA safety factor and 3x applied under FIFRA for toxicology data gaps. The FQPA safety factor for etridiazole is applied to chronic dietary risk assessment because uncertainty exists due to the lack of an acceptable multi-generation reproduction study in rats, which could identify potential toxicities following exposure to etridiazole in the offspring and/or the parental animals.
	UF=300 FQPA SF=3	
	Chronic RfD = 0.016 mg/kg/day    Chronic PAD = 0.005 mg/kg/day	
Chronic (Cancer) Dietary	Group B2 chemical - AProbable human carcinogen® - $Q_1^* = 3.33 \times 10^{-2} \text{ (mg/kg/day)}^{-1}$ in human equivalents [converted from animals to humans by use of the (mg/kg body weight) <sup>1</sup> cross species scaling factor].	
Dermal Absorption	A dermal absorption factor of 100% (default value)	

TABLE 3: SUMMARY OF TOXICOLOGY ENDPOINT AND DOSES FOR ETRIDIAZOLE (TERRAZOLE)		
EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT/STUDY/RATIONALE/UF/MOE
Short-Term (Dermal & Inhalation)	Oral NOAEL=15*	Reduced fetal body weights, decreased viability and external and skeletal malformations/variations in the rabbit developmental toxicity study. An adequate dose and endpoint for short-term dermal risk assessment could not be identified in two dermal toxicity studies classified by the HIARC as unacceptable as the result of the age of the studies and major deficiencies. Therefore, a developmental NOAEL from the developmental toxicity study in rabbits was selected because: 1) the developmental effects are considered short-term and thus are appropriate for this exposure period (i.e., 1-7 days) of concern, 2) the reproductive/fetal parameters are not evaluated in the dermal toxicity study and thus the consequences of these effects cannot be ascertained for the dermal route of exposure and 3) this endpoint will provide adequate protection for the subpopulation of females 13-50 years old (i.e. pregnant workers). Since no inhalation studies are available (with the exception of an acute inhalation toxicity study), an oral developmental NOAEL of 15 mg/kg/day would be protective of all population subgroups and is considered appropriate for short-term inhalation exposure (1 to 7 days) risk assessment.
Intermediate-Term (Dermal & Inhalation)	Oral NOAEL=4.8*	Increased absolute and relative liver weights, renal tubule cell karyomegaly, hepatocytomegaly and spongiosis hepatitis in the two-year carcinogenicity study in rats. This dose/endpoint was selected due to missing or unacceptable subchronic studies in the etridiazole data base. The developmental NOAEL (15 mg/kg/day) is not recommended for this time period since the lower NOAEL (4.8 mg/kg/day) in the two-year carcinogenicity study in rats is more protective/conservative for the intermediate-term dermal and inhalation exposure scenarios/risk assessments.
Long-Term (Dermal & Inhalation)	Oral NOAEL=4.8*	Increased absolute and relative liver weights, renal tubule cell karyomegaly, hepatocytomegaly and spongiosis hepatitis in the two-year carcinogenicity study in rats. This dose/endpoint was used for establishing the chronic RfD and is appropriate for long-term dermal and inhalation exposure scenarios/risk assessments.
MOE (Short-Term & Intermediate-Term)	A MOE of 100 is adequate for occupational exposure risk assessments. A MOE of 100 is required for non-occupational exposure risk assessments (adult golfers).	
MOE (Long-Term)	A MOE of 300 is required for occupational exposure risk assessments which includes the conventional 100x (10x for interspecies extrapolation and 10x for intraspecies variation and 3x applied under FIFRA for toxicology data gaps (i.e., the lack of acceptable chronic toxicology studies). There are no registered residential uses, therefore the FQPA safety factor is not required.	

\* Since an oral NOAEL was selected, a dermal absorption factor of 100% (default value) and an inhalation absorption factor of 100% (default value) should be used during route to route extrapolation.